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Case report

Pleural effusion: An uncommon manifestation of nitrofurantoin-induced pulmonary injury

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ABSTRACT

Nitrofurantoin has been documented as a cause of acute, sub-acute, and chronic pulmonary injury. This is a case of an 82 year-old female who presented with multiple episodes of respiratory symptoms due to recurrent pleural effusions after beginning nitrofurantoin therapy for urinary tract infection prophylaxis. Due to the rarity of pleural effusion as an adverse reaction to nitrofurantoin, the diagnosis was overlooked at first. This led to the patient undergoing multiple invasive procedures and accruing unnecessary healthcare cost before the diagnosis was made. This case demonstrates the need for physicians to remain mindful of rare adverse reactions from medications and maintain a high index of clinical suspicion with any patient presenting with a respiratory complaint while taking nitrofurantoin.

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1. Introduction

Nitrofurantoin has long been a staple for the treatment of urinary tract infections, either as a seven day course or as daily prophylaxis but recent guidelines has listed its use as potential first-line treatment of uncomplicated UTI. It has been an excellent alternative treatment for those with sulfa allergies, unable to tolerate trimethoprim-sulfamethoxazole. But, nitrofurantoin adverse events have been well documented throughout the literature for years. Most commonly nitrofurantoin causes gastrointestinal upset which includes nausea, vomiting, and diarrhea among others. Although rare, pulmonary adverse reactions have been the focus of many published works discussing the acute, subacute, and chronic effects of nitrofurantoin on the lungs [1,2]. A PubMed review of clinical cases over the last ten years found discussions of reactions including pulmonary fibrosis, interstitial pneumonitis, and hypersensitivity pneumonia [3,4]. When searching for nitrofurantoin-induced pleural disease, no cases have been documented since 2004 [5]. The objective of this report is to describe a rare but documented hypersensitivity reaction to nitrofurantoin in order to assist clinicians in identifying sequential relationships between symptoms and drug treatment to diagnose

adverse drug reactions in their patients sooner rather than later.

2. Case report

An 82 year old female presented to her primary care physician with symptoms of dyspnea and right-sided chest pain which had been ongoing for one week. The patient had been previously in good health prior to her presentation. Physical exam revealed decreased breath sounds at the right lung base with decreased fremitus but was negative for any other physical exam finding including a cutaneous rash, which has been linked to nitrofurantoin-induced Lupus. Her medical history included chronic urinary tract infections for which in the last month she had been placed on nitrofurantoin 100 mg daily for prophylaxis. Laboratory results from the initial presentation showed that the Anti-nuclear Antibody test (ANA) was negative which made a Lupus reaction less likely. An Erythrocyte Sedimentation Rate was checked but was within normal limits (32). Her ECG was normal and a transthoracic echocardiogram prior to her initial visit revealed normal heart structure and function with a left ventricular ejection fraction estimated at sixty percent. Therefore, cardiac cause was thought to be less likely and the patient was sent for a chest radiograph and thoracentesis with pleural fluid analysis for diagnosis. The radiograph showed significant right-sided pleural effusion. At that time she underwent a thoracentesis which removed 600 cc of clear fluid but ultimately did not find a cause for

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the effusion. (Table 1 shows pleural fluid analysis results). The patient was sent home with total resolution of her symptoms and a diagnosis of idiopathic pleural effusion. She was given an appointment with a pulmonologist, who also agreed in the diagnosis of idiopathic pleural effusion.

The patient remained in good health without recurrence of symptoms for one month. After one month, once again she began experiencing dyspnea and pain localized to the right chest and presented to her primary care physician. Physical exam yet again revealed decreased breath sounds at the right lung base with decreased fremitus. The patient was sent for a CT scan performed without contrast which revealed a mild to moderate right pleural effusion (Image 1).

A thoracentesis was then performed, removing another 600 cc of clear yellow tinted fluid. Still no etiology was identified. After the thoracentesis the patient yet again experienced total resolution of her dyspnea and chest pain.

Within the next two weeks, the patient experienced another urinary tract infection prompting her to visit the Urologist who had prescribed the nitrofurantoin. During her visit, her medication was switched to trimethoprim-sulfamethoxazole in order to treat this breakthrough UTI. Over the next three months, the patient was not prescribed nitrofurantoin. She did not develop any pulmonary symptoms throughout this time. At a follow up visit to her primary care physician during this three month window she was found to be asymptomatic and in good health without any signs or symptoms of a recurrent pleural effusion. After this time the patient began experiencing symptoms of a urinary tract infection and she was placed back on chronic nitrofurantoin at the same dosage for prophylactic treatment.

It took three weeks after restarting the nitrofurantoin therapy for the patient to begin experiencing similar symptoms of dyspnea and chest pain. She presented to her primary care physician with the same physical exam findings as was found previously. But at this visit, both the patient and her provider now had a higher degree of suspicion for a drug induced pleural effusion once the patient had recalled the three month asymptomatic period at which time the only change was the medication taken for UTI treatment. The recurrent episodes of pleural effusion at the same time the patient began taking nitrofurantoin and the resolution of symptoms once the medication was discontinued both met the Naranjo criteria of medication induced adverse reactions. It was at this time that the patient and her primary physician decided to discontinue the nitrofurantoin. A therapeutic thoracentesis was performed and withdrew 700 cc of clear pleural fluid. Fluid analysis still could not define a specific etiology and the patient was sent home asymptomatic with plans for close follow up.

One month following, the patient presented to her primary care physician for her follow up appointment. She continued to be asymptomatic, without any difficulty in breathing or chest pain. The patient also remained off nitrofurantoin and was now taking a different medication for urinary tract infections. A chest radiograph confirmed that the patient had total resolution of the pleural

Table 1
Pleural fluid chemistry.

Pleural fluid analysis			
Red Blood Cells	399	Segmented Neutrophils	17
White Blood Cells	1350	Glucose	127
Eosinophils	9	LDH	167
Lymphocytes	39	Protein	4
Monocytes	35	pH	7.51

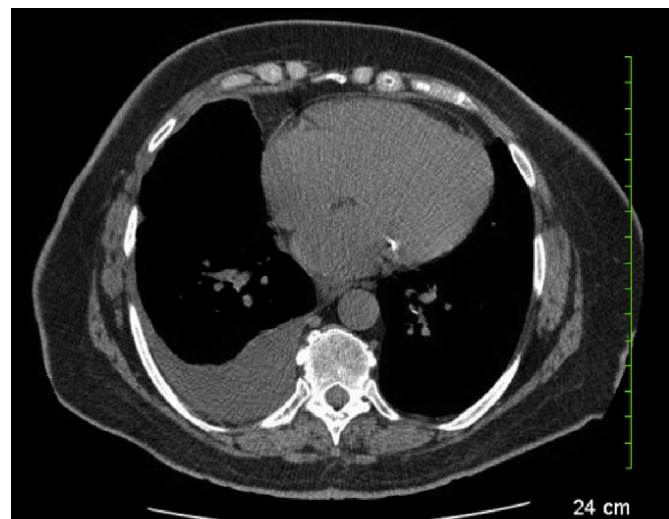


Image 1. CT Scan.

effusion. A transthoracic echocardiogram was performed and remained virtually unchanged from her previous study (TTE results found in Image 2). The patient was also referred to a pulmonologist at a tertiary care center who, after examining the patient and studying her records, agreed that the recurrent pleural effusion was indeed nitrofurantoin induced. After discontinuation of the medication the patient remained asymptomatic at all of her subsequent visits to her primary care physician.

3. Discussion

This case demonstrates a rarely documented adverse reaction to nitrofurantoin. Because pleural effusion is not often included as a potential pulmonary toxicity caused by nitrofurantoin therapy it can be easy for even the most experienced clinicians to neglect to tie the medication to the diagnosis. This case is evidence that an unexplained pleural disease, in the presence of nitrofurantoin use, should raise suspicion of a drug induced mechanism of injury.

This case scored highly on the Naranjo Scale indicating a high probability that the injury was a drug induced adverse reaction. The Naranjo Scale aids in making a diagnosis of drug induced adverse reaction when used in conjunction with clinical judgement. It is a useful tool in cases such as this when the mechanism of injury is rare and seemingly unexplained.

The case exhibits the need for physicians to remain mindful of rare adverse reactions from medications. This patient underwent multiple invasive procedures and accrued substantial healthcare cost all stemming from a reaction that resolved upon the discontinuation of a single medication. As this case proves, elderly patients are at an even higher risk of adverse reactions and drug interactions. The 2015 AGS Beers List recommended against the use of nitrofurantoin in the elderly. In those with renal impairment, the drug reaches higher systemic levels, increasing the risk for toxicities [6]. Polypharmacy is also a rather important issue in this age group which can further cloud the clinical picture. All of these factors provide further evidence for clinicians to perform a complete medication review when their patients present with unexplained symptoms, especially the elderly population. In doing so, the potential risk for harm will be lowered and patients will be less often subjected to invasive procedures which carry inherent risk of complication and increased cost.

BP: / HR: 68 Rhythm: Sinus Technical Quality: Fair

FINDINGS

Left Ventricle	Normal left ventricular size, systolic and diastolic function The left ventricular ejection fraction estimated at 65 %.
Right Ventricle	The right ventricle was normal in size and function.
Right Atrium	The right atrium was normal in size.
Left Atrium	The left atrium was enlarged
Mitral Valve	There is dense calcification of mitral annulus. There is good mobility of mitral leaflets. There is trace to mild mitral regurgitation seen to
Aortic Valve	Structurally normal aortic valve without sclerosis or stenosis. There is no aortic regurgitation.
Tricuspid Valve	Structurally normal tricuspid valve without prolapse or stenosis. There is trace tricuspid regurgitation. Right ventricular systolic pressure estimated to be 47 mm Hg.
Pulmonic Valve	Structurally normal pulmonic valve without significant stenosis or regurgitation.
Pericardium	Normal pericardium without effusion.
Great Vessels	The aortic root and ascending aorta is normal in size.

CONCLUSIONS

Normal left and right ventricular size and systolic function
 Normal left ventricular diastolic function
 Calcification of mitral annulus trace to mild mitral regurgitation
 Tricuspid regurgitation with moderate pulmonary hypertension
 Minimal left atrial enlargement

Image 2. TTE Results.

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Appendix

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